Letter to the Editor

Vaginal and Cervical Cancers and Other Abnormalities Associated with Exposure in Utero to Diethylstilbestrol and Related Synthetic Hormones

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The National Cancer Institute is supporting a study of vaginal cancer and other noncancerous genital tract irregularities in offspring of mothers who received synthetic estrogens during pregnancy. The study, entitled The DESAD Project (DES7 and Adenosis), seeks to provide answers concerning the risk to exposed offspring born after 1940 of developing cancer or other medically important conditions, including vaginal adenosis and cervical abnormalities. Each of 4 participating institutions8 is identifying 500 or more subjects with documented in utero exposure. Exposed daughters of different ages are being examined and followed to determine incidence and natural history of vaginal adenosis and other irregularities.

Abnormalities Associated with Exposure in Utero to DES

DES, a synthetic estrogen-type hormone, was first synthesized in the late 1930's. During the 40's many physicians in the United States and other countries prescribed this substance for pregnant women. Several studies suggested that in complications of pregnancy such as bleeding, threatened miscarriage, or diabetes, this treatment improved salvage of the fetus.

Later studies disclosed that the administration of DES during pregnancy was less effective than initially thought. Although its use in pregnancy has now been discontinued, DES remains a useful agent for certain menopausal symptoms, certain cases of carcinoma of the breast and prostate, and a few other clinical problems. A list of DES-type drugs is found in Table 1.

In 1971, Dr. Arthur L. Herbst, Dr. Howard Ulfelder, and Dr. David Poskanzer of Massachusetts General Hospital and the Harvard Medical School reported a link between maternal DES therapy during pregnancy and the later occurrence of clear-cell adenocarcinoma of the vagina in female offspring exposed to the drug in utero. This initial report was soon confirmed by others.

Soon after the discovery of the initial cases, a Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females was established by Dr. Herbst and Dr. Robert E. Scully with support from the National Cancer Institute and the American Cancer Society. It now contains varying amounts of data on almost 300 cases from the United States and abroad. The Registry address is MARP, Room 303, 5841 Maryland Avenue, Chicago, Ill. 60637.

The patients have ranged in age from 7 to 28 years at the time of diagnosis.

Documentation of exposure to DES-type hormones has been established in two-thirds of the fully investigated case histories. Of the vaginal adenocarcinoma cases, more than 80% are known to have been exposed to DES-type hormones. Because DES-type hormones were not administered to some of the mothers of these cancer patients, factors other than maternal hormone administration may also play a role in the etiology of these cancers.

In all cases for which precise treatment dates are available, the drug was initiated before the 18th week of gestation. Dosages and duration of therapy varied widely. However, as little as 1.5 mg DES administered daily throughout pregnancy was found in 1 case history to be associated with subsequent cancer in female offspring. Administration of the drug in varying amounts for a week or more during the 1st trimester also was associated with the subsequent development of cancer.

Cancers related to DES exposure have not been reported in male offspring.

Although the exact number of pregnant women treated with DES or chemically similar compounds during pregnancy is unknown, it has been estimated to be as many as 2
Nonsteroidal estrogen-progesterone combinations

Amperone
Di-Erone
Estan
Metystil

Pro gravidium

Vaginal cream-suppositories with nonsteroidal estrogens

AVC cream with Dienestrol
Dienestrol cream

Table 1

DES-type drugs that may have been prescribed to pregnant women

Nonsteroidal estrogens
Benazestrol
Chlorotriamene
Comestrol
Cyren A
Cyren B
Delval
DES
Desplex
Diestrol
Dibistil
Dienestrol
Dienoestrol
Diethylstilbestrol dipalmitate
Diethylstilbestrol diphenolate
Diethylstilbestrol dipropionate
Diethylstilbestrol diphosphate
Dienoestrol
Dienestrol
Domestrol
Estilben
Estrobene
Estrobene DP.
Estrosyn
Fontol
Gynben
Gyneben
Hexestrol
Hexoestrol
Hi-Bestrol
Menocin
Menpran
Mesilbol
Methallenesil
Microest
Mikarol

Nonsteroidal estrogen-androgen combinations

Amperone
Di-Erone
Estan
Metystil

Management of Females Exposed to DES-type Drugs

All asymptomatic girls who were exposed in utero should receive a thorough pelvic examination at menarche or if they have reached 14 years of age. Younger girls should be examined if they develop abnormal bleeding or discharge. Whenever prenatal exposure is probable and there are symptoms of discharge, further investigation is imperative, regardless of the patient's age. This investigation should not be concluded until it is certain that no lesion is present.

Before the examination is undertaken, the entire procedure should be thoroughly discussed with the patient (and her mother or father if she is a minor).

The examination should include inspection and palpation, Papanicolau smear (cervix and vagina), and a iodine staining test of the entire cervix and vagina. Abnormal areas, including those that do not stain with iodine, should be biopsied. This procedure can be performed in the physician's office with small biopsy instruments and without significant discomfort.

For the very young patient who has symptoms that require investigation, anesthesia may occasionally be required before an examination. A small speculum permits adequate visualization of the vagina without undue discomfort in younger patients.

With asymptomatic females, if adequate examination is not possible at the initial visit, vaginal tampons should be used for a few months to allow an adequate examination later without discomfort. Colposcopy is a useful adjunct to this examination, but it is not essential. Utilizing its low-power magnification to examine the vagina and cervix, the physician can identify areas of glandular tissue (adenosis) in the vagina or on the cervix. This identification permits directed rather than "blind" biopsies. When used in conjunction with the iodine staining test and selected biopsy, colposcopy permits precise recording of observed abnormalities and their appraisal at fixed intervals.

The patient exposed to DES-type drugs should be followed on a regular basis. After a normal initial examination, annual pelvic examinations with cervical and vaginal cytology and iodine staining are probably adequate. If any abnormalities are noted during the initial evaluation, more frequent follow-up examinations are suggested (every 3 to 6 months, depending on the severity of the findings).

Locally destructive measures such as cautery, cryosurgery, or excision can be utilized if atypical changes such as marked squamous dysplasia or carcinoma in situ of...
the vagina or cervix are found on biopsy.

Optimal management of nonmalignant lesions in females exposed to DES-type drugs in utero is uncertain. At the present time, no case has been reported in which vaginal adenosis has progressed to cancer under direct observation. Careful follow-up appears at present to be the most prudent approach to DES-exposed subjects without carcinoma.

To date, there is no evidence indicating that use of oral contraceptives by the DES-exposed population would be undesirable. However, they do add additional hormonal variables to a complex situation and are one more aspect of the problem that requires further information.

The presence of adenosis is not a contraindication to future pregnancy, in case the woman desires to have children.

Decisions regarding mode and extent of therapy in these young women are difficult in themselves and are further complicated by emotionally charged issues. Both surgery and high-energy radiotherapy can potentially cure the disease. Cancers associated with DES-type drugs may develop in young women primarily in tissues of Mullerian origin: the upper portion of the vagina and the cervix.

Treatment should be highly individualized and is best accomplished by physicians experienced in treating gynecological cancers.

A useful bibliography on the subject of DES exposure in utero follows. Readers desiring further information may obtain without charge 3 publications from the Office of Cancer Communications, National Cancer Institute, by using the card enclosed in this issue of CANCER RESEARCH.

BIBLIOGRAPHY

Vaginal and Cervical Cancers and Other Abnormalities Associated with Exposure in Utero to Diethylstilbestrol and Related Synthetic Hormones

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